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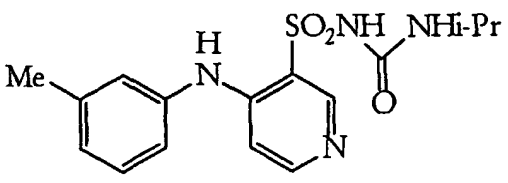
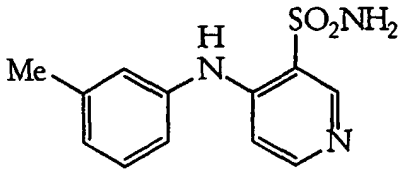
(54) Title: PROCESS FOR THE PREPARATION OF HIGHLY PURE TORSEMIDE



[1]



[2]

(57) Abstract: The present invention provides a novel process for the preparation of highly pure torsemide [1] by reacting of 4-m-tolylamino-3-pyridinesulfonamide [2] with phenyl isopropylcarbamate in the presence of lithium base (FI, II). The present invention also provides a novel intermediate - torsemide lithium, also in hydrate or solvate form - which is a stable, solid compound, and may be simply isolated from the reaction mixture to give after acidification practically pure torsemide [1] without further purification steps.

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PROCESS FOR THE PREPARATION OF HIGHLY PURE TORSEMIDE

FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of diuretics such as torsemide and precursors thereof, to novel intermediates used in this process and to the preparation thereof.

LIST OF REFERENCES

The following references are considered to be pertinent for the purpose of understanding the background of the present invention:

J. Delarge, Ann. Pharm. Fr., **1973**, v. 31, 467;

J. Delarge, Arzneim.-Forsch./Drug Res., **1988**, v. 38, 144;

DE 2054142;

US 4,018,929;

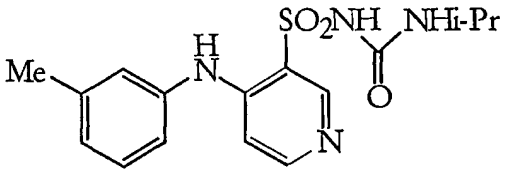
US 4,123,450;

US 6,310,214;

WO 01/70226.

BACKGROUND OF THE INVENTION

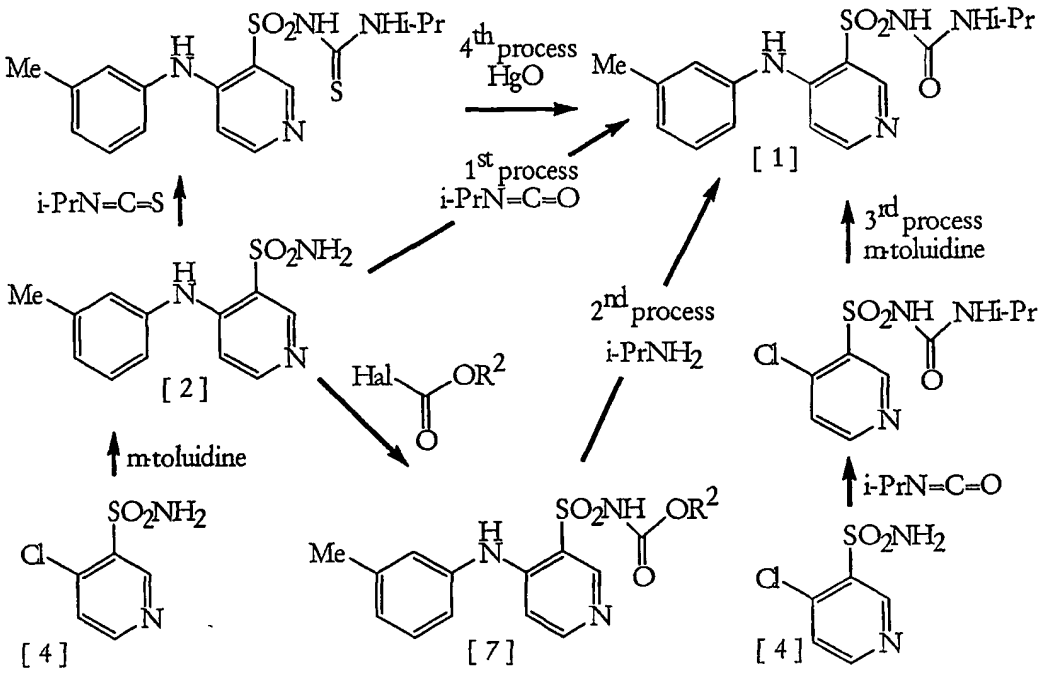
Torsemide (also known as torasemide) (N-[(isopropylamino)-carbonyl]-4-(*m*-tolylamino)-3-pyridinesulfonamide) **[1]**



[1]

is a powerful diuretic which may be used for the treatment of hypertension and heart failure (Delarge, 1988 and U. S. Patent No. 4,018,929).

Delarge (1988) and US 4,018,929 provide four processes for the preparation of torsemide **[1]** from 4-chloro-3-pyridinesulfonamide **[4]**, as shown in Scheme 1 below:

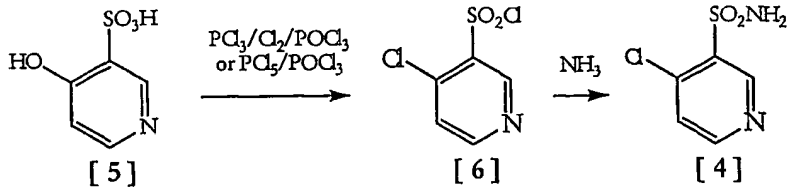


R^2 represents a C1-C4-alkyl group

Scheme 1

It should be noted that it might be difficult to remove the trace amounts of heavy metals from the final product in 4th process of torsemide production. In addition, isopropyl isocyanate and isopropyl isothiocyanate used in the 1st, 3rd and 4th processes are unstable and toxic reagents. On the other hand, the 2nd process of torsemide production may be carried out only at high pressure because of the combination of low reactivity of compound [7] and low boiling point (33-34 °C) of isopropylamine.

The starting material for the torsemide syntheses - 4-chloro-3-pyridinesulfonamide [4] - is, in turn, prepared from 4-hydroxy-3-pyridinesulfonic acid [5] according to Scheme2:



Scheme 2

Delarge (1973) describes a process for the preparation of 4-chloro-3-pyridinesulfonyl chloride **[6]** starting from 4-hydroxy-3-pyridinesulfonic acid **[5]**, and using a mixture of PCl_5 and $POCl_3$. The excess of $POCl_3$ and PCl_5 is removed by vacuum distillation, and the remaining residue is worked up in a complex manner. Similar processes are known from the literature (see WO 01/70226; DE 2054142).

The chlorination showed in the above Scheme 2 takes place in one step by substituting both the OH-group bound to the ring and the OH of the sulfonic acid residue, with formation of hydrogen chloride and $POCl_3$. Phosphorus pentachloride is used in excess, as chlorination agent, whereas phosphorous oxychloride is used as a solvent since it is also formed as a by product in the reaction mixture. After the reaction, phosphorous oxychloride can be removed from the mixture by distillation. Other chlorination agents, for example, phosphorous trichloride, essentially replace only the phenolic OH group and are, therefore, not suitable for the reaction.

One of the drawbacks when using phosphorous oxychloride is that at the end of the chlorination it can't be fully removed from the reaction mass by distillation because the residue becomes very viscous (or some times solid) at the end of the distillation process. Also, since phosphorus pentachloride is used in excess, unreacted phosphorus pentachloride sublimes during the distillation of the solvent phosphorous oxychloride ($POCl_3$), causing to encrustations and stoppages of the reaction equipment.

It is another disadvantage of the known processes that, in the case of batches of large-scale size, the starting materials cannot be mixed together from the beginning, since this may lead to a longer controllable course of the reaction with a vigorous evolution of gas. Therefore, according to the prior art, the acid [5] is slowly added to the boiling mixture of phosphorus pentachloride and phosphorus oxychloride, with possible after-dosing of PCl_5.

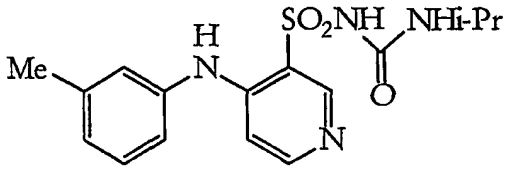
The dosing in of the solid reactants (4-hydroxy-3-pyridinesulfonic acid [5] and PCl_5) in the known processes leads to considerable technical problems. Also, using gaseous chlorine and PCl_3 to form in situ PCl_5, as described in US 6,310,214 creates environmental and safety problems.

SUMMARY OF THE INVENTION

The present invention provides a new process for the preparation of highly pure torsemide **[1]**, which uses stable intermediates and avoids the use of high-pressure equipment and heavy metals.

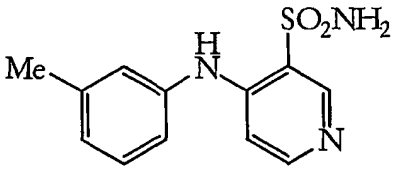
The present invention also provides a new process for the preparation of 4-chloro-3-pyridinesulfonamid **[4]** that is technically simple and affords the product in high yield.

Thus, the present invention provides, according to an aspect thereof, a process for the preparation of highly pure torsemide **[1]**

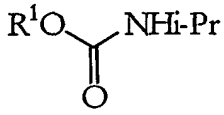


[1]

which process comprises reacting, optionally in the presence of base, 4-*m*-tolylamino-3-pyridinesulfonamide **[2]** or a salt thereof with isopropylcarbamate **[3]**



[2]



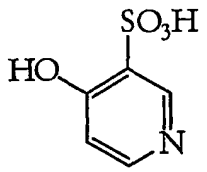
[3]

wherein R^1 represents an aryl group, the aryl group being possibly substituted by one or more substituents selected from the C1-C4-alkyl, alkoxy, halo, trifluoromethyl and nitro. Preferably, the aryl is phenyl.

At times, a base is used in the process of the invention. Examples of suitable bases are lithium bases such as lithium hydroxide, lithium carbonate and the like. More preferably the base is lithium hydroxide.

Isopropylcarbamates of formula **[3]** are stable, solid compounds, obtainable in high yield by reaction of aryl chloroformate with isopropylamine (US 4,123,450), which can be easily purified by crystallization and stored for long periods of time.

In the above process, compound **[2]** is obtained from 4-chloro-3-pyridinesulfonamide **[4]**, which in turn is prepared from 4-hydroxy-3-pyridinesulfonic acid **[5]**,



[5]

and phosphorus pentachloride.

It was surprisingly found in the present invention, that the use of chlorobenzene as solvent in the chlorination of 4-hydroxy-3-pyridinesulfonic acid **[5]** allows mixing together the starting materials (4-hydroxy-3-pyridinesulfonic acid **[5]** and PCl_5) without any evolution of gaseous hydrogen chloride at a temperature in the range of 0 – 40 °C and with controllable evolution of gas by stirring the mixture with heating at a temperature higher than 80 °C. Using chlorobenzene as solvent also allows to fully complete the reaction and remove phosphorous oxychloride by distillation from the reaction mass after chlorination.

According to a preferred embodiment, the process of the present invention for the preparation of torsemide **[1]** comprises the steps of:

(a) reacting a basic aqueous solution of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]** with isopropylcarbamate **[3]** in the presence of an organic solvent and, optionally, purifying the obtained salt of torsemide **[1]**; and

(b) acidifying the torsemide salt, prepared in step (a), to obtain highly pure torsemide **[1]**.

The term *"highly pure"* relates to torsemide, which has a liquid chromatography purity (relative area method) of more than 99.8 % with content of any individual impurity not exceeding 0.1 area %.

The molar ratio between 4-*m*-tolylamino-3-pyridinesulfonamide **[2]** and aryl isopropylcarbamate **[3]** is preferably between about 1:1 and 1:3. More preferably, the molar ratio is between 1:1.1 and 1:1.5.

According to another preferred embodiment, the process of the present invention for the preparation of highly pure torsemide **[1]** comprises the steps of:

(a) reacting 4-chloro-3-pyridinesulfonamide **[4]** with *m*-toluidine in aqueous media, basifying the reaction mixture and, optionally, purifying the prepared basic aqueous solution of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**;

(b) reacting the basic aqueous solution of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]** obtained in step (a) without isolating the compound **[2]** with aryl isopropylcarbamate **[3]** in the presence of organic solvent and, optionally, purifying the prepared salt of torsemide **[1]**;

(c) acidifying the torsemide salt obtained in step (b), to obtain highly pure torsemide **[1]**.

According to a further preferred embodiment, the process for the preparation of torsemide **[1]** comprises the steps of:

(a) reacting of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]** with isopropylcarbamate **[3]** in the presence of water, organic solvent and lithium base selected from lithium hydroxide, lithium carbonate, lithium bicarbonate and mixtures thereof, to precipitate lithium torsemide in solid form;

(b) filtering the precipitated lithium torsemide obtained in step (a) and, optionally, purifying the lithium torsemide by recrystallizing, trituring or/and reslurring;

(c) acidifying lithium torsemide obtained in step (b), to form highly pure torsemide **[1]**.

Preferably, the isopropylcarbamate **[3]** is phenyl isopropylcarbamate or nitrophenyl isopropylcarbamate. Most preferably, the isopropylcarbamate **[3]** is phenyl isopropylcarbamate.

It has been surprisingly found by the inventors that isolation and purification of torsemide is greatly facilitated by conversion of torsemide or one of its salts into lithium torsemide and precipitation of the latter, normally in crystalline form. Such precipitation can be effected, possibly due to the surprisingly high affinity of torsemide anions to lithium cations, with little or no significant co-precipitation of impurities.

In accordance with another preferred embodiment, the process for the preparation of highly pure torsemide **[1]** comprises the steps of:

(a) mixing 4-hydroxy-3-pyridinesulfonic acid **[5]**, phosphorus pentachloride and chlorobenzene at 0 – 40 °C and heating the mixture at 80 – 150 °C with stirring;

(b) removing by distillation any phosphorous oxychloride formed;

(c) adding the resulting solution of 4-chloro-3-pyridinesulfochloride **[6]** in chlorobenzene to ammonia;

(d) evaporating any ammonia excess from the reaction mixture obtained in step (c) and isolating the precipitated solid 4-chloro-3-pyridinesulfonamide **[4]** by filtration;

(e) reacting 4-chloro-3-pyridinesulfonamide **[4]** prepared in step (d) with excess of *m*-toluidine in aqueous media;

(f) adding a lithium base selected from lithium hydroxide, carbonate, bicarbonate and mixtures thereof to the mixture of step (e) and removing any un-reacted *m*-toluidine by extraction to obtain an aqueous solution of the lithium salt of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**;

(g) reacting the aqueous solution of the lithium salt of **[2]** obtained in step (f) with isopropylcarbamate **[3]** in the presence of organic solvent to precipitate lithium torsemide and, optionally, purifying the lithium torsemide by recrystallizing, trituring or/and reslurring;

(h) isolating the precipitated solid lithium torsemide prepared in step (g) by filtration; and

(j) acidifying lithium torsemide prepared in step (h), to yield highly pure torsemide **[1]**.

Examples of suitable organic solvents to be used in the above processes are aliphatic ketones or aliphatic alcohols. Examples of aliphatic ketones are acetone, methyl ethyl ketone (MEK), diethyl ketone, methyl isopropyl ketone, methyl isobutyl ketone (MIBK) and the like. Examples of aliphatic alcohols are methanol, ethanol, isopropanol or butanol.

Preferably, the conversion of lithium torsemide to torsemide **[1]** comprises the steps of:

(i) neutralizing of solution of lithium torsemide in DMSO with acid

(ii) mixing the solution obtained in step (i) with water and

(iii) filtering off precipitated torsemide **[1]**.

In accordance with another aspect of this invention, the present invention provides lithium salt of torsemide, including hydrates and solvates thereof, in solid form. This novel compound is obtained as an intermediate in the process of the present invention. It is a stable, solid compound, which may be simply isolated from the reaction mixture by filtration to give after acidification practically pure (by HPLC) torsemide without further purification steps.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 schematically shows a perspective view of torsemide lithium hydrate molecule and the atomic numbering of non-hydrogen atoms as derived from single crystal X-ray analysis. (Atomic coordinates based on Table 2).

Figure 2 shows a characteristic X-ray powder diffraction pattern of torsemide lithium hydrate obtained in the present invention. Vertical axis: intensity (CPS); Horizontal axis: 2θ (degrees).

Figure 3 shows calculated X-ray powder diffraction pattern of crystalline torsemide lithium hydrate. Vertical axis: intensity (CPS); Horizontal axis: 2θ (degrees).

Figure 4 shows the infrared spectrum of torsemide lithium hydrate of the present invention in potassium bromide.

Figure 5 shows the differential scanning calorimetry (DSC) thermogram of torsemide lithium hydrate.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the present invention provides a process for the preparation of torsemide **[1]** that comprises the steps of reacting a basic aqueous solution of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]** with isopropylcarbamate of formula **[3]**.

Preferably, isopropylcarbamate **[3]** is phenyl isopropylcarbamate or nitrophenyl isopropylcarbamate. Most preferably, isopropylcarbamate **[3]** is phenyl isopropylcarbamate. Phenyl isopropylcarbamate may be prepared by reacting phenyl chloroformate and isopropylamine by a reaction similar to that described in US 4,123,450 (see for example Example 8) but using heptane as the solvent instead of methylene chloride. The use of heptane as the solvent in all the synthesis steps: in the reaction, in the work-up of the reaction mixture and in the crystallization of the desired product represents a considerable advantage. Preferably, the process for the preparation of phenyl isopropylcarbamate with high yield and purity comprises the steps of:

(a) reacting phenyl chloroformate and isopropylamine in the presence of heptane as solvent;

(b) basifying the mixture obtained in step (a) with aqueous alkali;

(c) separating the organic layer from the mixture obtained in step (b);

(d) washing the organic phase obtained in the step (c) with water and azeotropic drying of the wet organic phase;

(e) crystallizing the desired phenyl isopropylcarbamate from the heptane solution and, optionally, recrystallizing the product from heptane.

4-Chloro-3-pyridinesulfonamide **[4]** may be prepared from 4-hydroxy-3-pyridinesulfonic acid **[5]**. Preferably, the chlorination reaction of 4-hydroxy-3-pyridinesulfonic acid **[5]** is carried out in the presence of

chlorobenzene as solvent. This allows mixing together the starting materials (4-hydroxy-3-pyridinesulfonic acid **[5]** and PCl_5) without any evolution of gaseous hydrogen chloride at 0 – 40 °C and with controllable evolution of gaseous hydrogen chloride when heating at 80 – 150 °C. Using chlorobenzene as solvent also allows to fully complete the reaction and remove phosphorous oxychloride by distillation from the reaction mass after the chlorination reaction and using the fluid residue (solution of 4-chloro-3-pyridinesulfochloride **[6]** in chlorobenzene) per se after distillation step in the next amidation step.

It has been surprisingly found by the inventors that isolation and purification of torsemide is greatly facilitated by conversion of torsemide or one of its salts into the lithium salt of torsemide and precipitation of the latter, in solid form. Such purification can be effected, possibly due to surprisingly high affinity of torsemide anions to lithium cations, with little or no significant co-precipitation of impurities. Lithium torsemide may be amorphous but preferable, it is in crystalline form. Lithium torsemide can also be isolated in solvent adduct form.

A preferred process for the preparation of torsemide **[1]** is shown in Scheme 3 below and comprises the steps of:

(a) mixing of 4-hydroxy-3-pyridinesulfonic acid **[5]**, phosphorus pentachloride and chlorobenzene at 0 – 40 °C and stirring the mixture while heating at 80 – 150 °C;

(b) removing any phosphorous oxychloride formed by distillation;

(c) adding the resulting solution of 4-chloro-3-pyridinesulfochloride **[6]** in chlorobenzene to ammonia;

(d) evaporating any ammonia excess from the reaction mixture prepared in step (c) and isolating the precipitated solid 4-chloro-3-pyridinesulfonamide **[4]** by filtration;

(e) reacting the 4-chloro-3-pyridinesulfonamide **[4]** prepared in step (d) with excess of *m*-toluidine in aqueous media;

(f) adding lithium hydroxide, carbonate, bicarbonate or mixture thereof to the mixture of step (e) and removing any un-reacted *m*-toluidine by extraction, to obtain an aqueous solution of the lithium salt of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**;

(g) reacting the aqueous solution of the lithium salt of **[2]** obtained in step (f) with isopropylcarbamate **[3]** in the presence of organic solvent to precipitate torsemide lithium hydrate;

(h) isolating the precipitated solid lithium torsemide prepared in step (g) by filtration and, optionally, purifying the lithium torsemide by recrystallizing, trituring or/and reslurring;

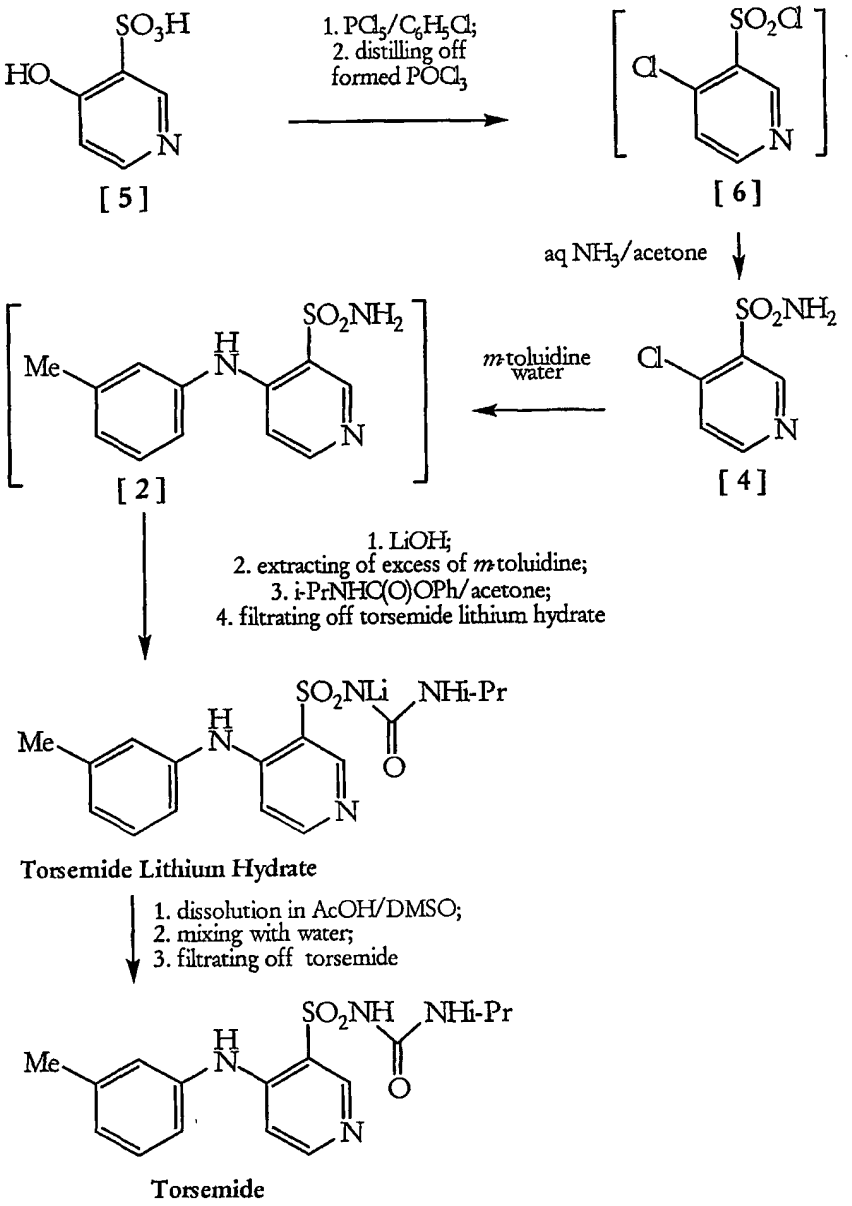
(j) acidifying of lithium torsemide, prepared in step (h), to yield highly pure torsemide **[1]**.

Preferably, the conversion of lithium torsemide to torsemide **[1]** comprises the steps of:

(i) dissolving lithium torsemide in a solvent system comprising acetic acid and dimethyl sulfoxide (AcOH/DMSO);

(ii) mixing the solution, obtained on step (i), with water and

(iii) filtering off precipitated torsemide **[1]**.



Scheme 3

In accordance with another aspect of this invention, the present invention provides lithium salt of torsemide in solid form. Lithium torsemide is stable solid compound, which can be further optionally purified by recrystallizing, triturating or/and reslurring and stored for long period of time.

Lithium torsemide may also exist in solvate adduct form. Preferably the solvent is water, ethanol, isopropanol or isobutanol.

Lithium torsemide solvent adduct may be prepared, for example, in the process of purification of lithium torsemide comprising the step of:

א) mixing a solution of the lithium salt of torsemide in DMSO with solvent until solvent adduct of the lithium salt of torsemide begins to precipitate;

ב) filtering the precipitated lithium salt of torsemide solvent adduct;

The organic solvents used in the above processes are aliphatic alcohols. Examples of aliphatic alcohols are ethanol, isopropanol or isobutanol.

The present invention further provides torsemide lithium hydrate. Torsemide lithium hydrate is a novel compound obtained as an intermediate in the novel process of the invention. This novel compound is a stable, solid compound, which may be simply isolated from the reaction mixture by filtration to give after acidification practically pure (by HPLC) torsemide without further purification steps.

The crystalline state of a compound can be described by several crystallographic parameters: unit cell dimensions, space group and atomic position of all atoms in the compound relative to the origin of its unit cell. These parameters are experimentally determined by single crystal X-ray analysis. The crystal structure of torsemide lithium hydrate has been determined at 293 K. The unit cell parameters are shown in Table 1.

Table 1 Crystal parameters of torsemide lithium hydrate

Formula	$C_{16}H_{21}LiN_4O_4S$
Formula weight (amu)	382.37
Space group	P $2_1/c$
Cell dimensions	
a (Å)	12.401
b (Å)	15.640
c (Å)	9.408
α (°)	90.00
β (°)	94.22
γ (°)	90.00
V ($Å^3$)	1819.7
Z (molecules/units cell)	4
Density (g/cm^3)	1.359

The unit cell dimension is defined by three parameters: length of the sides of the cell, relative angles of sides to each other and the volume of the cell. The lengths of the sides of the unit cell are defined by a, b and c. The relative angles of the cell sides are defined by α, β and γ. The volume of the cell is defined as V.

This invention also relates to the crystalline torsemide lithium hydrate having a single X-ray crystallographic analysis, which yields atomic positions of all atoms relative to the origin of the unit cell as showed in Tables 2 through 6, and as represented in Fig. 1. Tables 2 through 6 list the parameters of atomic coordinates, and their isotropic thermal parameters, bond lengths, bond angles, anisotropic thermal parameters, and proton atom coordinates and their isotropic thermal parameters.

Table 2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3). U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U (eq)
S(1)	5560(1)	1636(1)	2447(1)	35(1)
O(1)	4824(2)	1205(2)	1429(3)	43(1)
O(2)	5069(2)	2263(2)	3342(3)	41(1)
O(3)	7244(2)	2817(2)	3443(3)	41(1)
O(4)	5777(3)	4327(2)	3718(3)	56(1)
N(1)	6948(4)	98(3)	1716(4)	48(1)
N(2)	6308(3)	310(2)	6009(4)	49(1)
N(3)	6476(3)	2005(2)	1537(3)	34(1)
N(4)	8017(3)	2785(3)	1354(4)	42(1)
C(1)	8504(4)	-1098(3)	-832(5)	51(1)
C(2)	8109(4)	-448(3)	-13(4)	48(1)
C(3)	7371(4)	-621(3)	985(4)	42(1)
C(4)	7018 (4)	-1443(3)	1202(5)	51(1)
C(5)	7419(4)	-2092(3)	389(5)	57(1)
C(6)	8126(4)	-1923(3)	-614(5)	57(1)
C(7)	9320(5)	-915(4)	-1898(6)	75(2)
C(8)	6724(4)	146(3)	3097(4)	38(1)
C(9)	6141(3)	856(3)	3612(4)	35(1)
C(10)	5973(4)	902(3)	5036(4)	42(1)
C(11)	6838(4)	-356(3)	5514(5)	55(1)
C(12)	7072(4)	-467(3)	4138(4)	49(1)
C(13)	7243(3)	2549(3)	2199(4)	33(1)
C(14)	8758(4)	3507(3)	1702(5)	44(1)
C(15)	9611(4)	3276(4)	2857(5)	62(2)
C(16)	9241(4)	3780(4)	357(5)	64(2)
Li(1)	5930(6)	3182(5)	4368(7)	42(2)

Table 3 Bond lengths (Å)

S(1)-O(1)	1.440(3)	C(3)-C(4)	1.379(6)
S(1)-O(2)	1.455(3)	C(4)-C(5)	1.385(6)
S(1)-N(3)	1.581(3)	C(4)-H(4)	0.9300
S(1)-C(9)	1.760(4)	C(5)-C(6)	1.360(7)
S(1)-Li(1)#1	3.033(7)	C(5)-H(5)	0.9300
S(1)-Li(1)	2.980(6)	C(6)-H(6)	0.9300
O(1)-Li(1)#1	2.637(7)	C(7)-H(7A)	0.9600
O(2)-Li(1)	1.996(8)	C(7)-H(7B)	0.9600
O(3)-C(13)	1.243(4)	C(7)-H(7C)	0.9600
O(3)-Li(1)	1.987(8)	C(8)-C(12)	1.415(6)
O(4)-Li(1)	1.897(8)	C(8)-C(9)	1.428(6)
O(4)-H(1O4)	0.91(3)	C(9)-C(10)	1.372(5)
O(4)-H(2O4)	0.88(3)	C(10)-H(10)	0.9300
N(1)-C(8)	1.350(5)	C(11)-C(12)	1.359(6)
N(1)-C(3)	1.438(5)	C(11)-H(11)	0.9300
N(1)-H(1N1)	0.81(3)	C(12)-H(12)	0.9300
N(2)-C(11)	1.334(6)	C(14)-C(16)	1.502(6)
N(2)-C(10)	1.347(5)	C(14)-C(15)	1.504(6)
N(3)-C(13)	1.390(5)	C(14)-H(14)	1.05(4)
N(3)-Li(1)#1	2.123(7)	C(15)-H(15A)	0.9600
N(4)-C(13)	1.342(5)	C(15)-H(15B)	0.9600
N(4)-C(14)	1.477(6)	C(15)-H(15C)	0.9600
N(4)-H(1N4)	0.83(3)	C(16)-H(16A)	0.9600
C(1)-C(2)	1.386(6)	C(16)-H(16B)	0.9600
C(1)-C(6)	1.393(7)	C(16)-H(16C)	0.9600
C(1)-C(7)	1.504(6)	Li(1)-O(1)#2	2.637(7)
C(2)-C(3)	1.386(6)	Li(1)-N(3)#2	2.123(7)
C(2)-H(2)	0.9300	Li(1)-S(1)#2	2.980(6)

Table 4 Bond Angles (°)

O(1)-S(1)-O(2)	115.37(19)
O(1)-S(1)-N(3)	104.83(17)
O(2)-S(1)-N(3)	114.55(18)
O(1)-S(1)-C(9)	107.45(19)
O(2)-S(1)-C(9)	106.08(17)
N(3)-S(1)-C(9)	108.2(2)
O(1)-S(1)-Li(1)#1	62.21(19)
O(2)-S(1)-Li(1)#1	126.80(19)
N(3)-S(1)-Li(1)#1	43.15(19)
C(9)-S(1)-Li(1)#1	125.9(2)
O(1)-S(1)-Li(1)	146.1(2)
O(2)-S(1)-Li(1)	33.83(19)
N(3)-S(1)-Li(1)	87.07(18)
C(9)-S(1)-Li(1)	98.31(19)
Li(1)#1-S(1)-Li(1)	118.41(12)
S(1)-O(1)-Li(1)#1	88.9(2)
S(1)-O(2)-Li(1)	122.2(3)
C(13)-O(3)-Li(1)	124.4(3)
Li(1)-O(4)-H(1O4)	119(3)
Li(1)-O(4)-H(2O4)	135(3)
H(1O4)-O(4)-H(2O4)	105(5)
C(8)-N(1)-C(3)	127.7(4)
C(8)-N(1)-H(1N1)	121(4)
C(3)-N(1)-H(1N1)	111(4)
C(11)-N(2)-C(10)	115.8(4)
C(13)-N(3)-S(1)	118.4(3)
C(13)-N(3)-Li(1)#1	132.4(3)
S(1)-N(3)-Li(1)#1	106.2(3)
N(4)-C(14)- C(13)	122.6(4)
C(13)-N(4)-H(1N4)	124(3)
C(14)-N(4)-H(1N4)	109(3)
C(2)-C(1)-C(6)	117.5(4)
C(2)-C(1)-C(7)	120.9(5)

C(6)-C(1)-C(7)	121.6(5)
C(1)-C(2)-C(3)	120.7(5)
C(1)-C(2)-H(2)	119.6
C(3)-C(2)-H(2)	119.6
C(4)-C(3)-C(2)	121.0(4)
C(4)-C(3)-N(1	121.8(4)
C(2)-C(3)-N(1)	117.0(4)
C(3)-C(4)-C(5)	118.1(4)
C(3)-C(4)-H(4)	121.0
C(5)-C(4)-H(4)	121.0
C(6)-C(5)-C(4)	121.1(5)
C(6)-C(5)-H(5)	119.4
C(4)-C(5)-H(5)	119.4
C(5)-C(6)-C(1)	121.5(5)
C(5)-C(6)-H(6)	119.2
C(1)-C(6)-H(6)	119.2
C(1)-C(7)-H(7A)	109.5
C(1)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(1)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
N(1)-C(8)-C(12)	123.6(4)
N(1)-C(8)-C(9)	121.0(4)
C(12)-C(8)-C(9)	115.3(4)
C(10)-C(9)-C(8	119.3(4)
C(10)-C(9)-S(1)	119.1(3)
C(8)-C(9)-S(1)	121.5(3)
N(2)-C(10)-C(9)	124.5(4)
N(2)-C(10)-H(10)	117.8
C(9)-C(10)-H(10)	117.8
N(2)-C(11)-C(12)	125.3(4)
N(2)-C(11)-H(11)	117.4
C(12)-C(11)-H(11)	117.4
C(11)-C(12)-C(8)	119.8(4)

C(11)-C(12)-H(12)	120.1
C(8)-C(12)-H(12	120.1
O(3)-C(13)-N(4)	120.9(4)
O(3)-C(13)-N(3)	125.6(4)
N(4)-C(13)-N(3)	113.5(3)
N(4)-C(14)-C(16)	108.2(4)
N(4)-C(14)-C(15)	111.7(4)
C(16)-C(14)-C(15)	111.9(4)
N(4)-C(14)-H(14)	102(2)
C(16)-C(14)-H(14)	114(2)
C(15)-C(14)-H(14)	108(2)
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(14)-C(16)-H(16A)	109.5
C(14)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(14)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
O(4)-Li(1)-O(3)	101.3(3)
O(4)-Li(1)-O(2)	119.1(4)
O(3)-Li(1)-O(2)	90.5(3)
O(4)-Li(1)-N(3)#2	117.2(4)
O(3)-Li(1)-N(3)#2	99.7(4)
O(2)-Li(1)-N(3)#2	119.2(4)
O(4)-Li(1)-O(1)#2	81.3(3)
O(3)-Li(1)-O(1)#2	156.1(4)
O(2)-Li(1)-O(1)#2	109.2(3)
N(3)#2-Li(1)-O(1)#2	59.28(18)
O(4)-Li(1)-S(1)#2	101.8(3)
O(3)-Li(1)-S(1)#2	130.0(3)

O(2)-Li(1)-S(1)#2	115.1(3)
N(3)#2-Li(1)-S(1)#2	30.62(13)
O(1)#2-Li(1)-S(1)#2	28.90(9)
O(4)-Li(1)-S(1)	123.6(3)
O(3)-Li(1)-S(1)	66.6(2)
O(2)-Li(1)-S(1)	23.94(12)
S(1)#2-Li(1)-S(1)	128.9(2)
N(3)#2-Li(1)-S(1)	119.1(3
O(1)#2-Li(1)-S(1)	131.6(3)

Table 5. Anisotropic displacement parameters ($Å^2 \times 10^3$)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1)	45(1)	27(1)	32(1)	0(1)	4(1)	0(1)
O(1)	52(2)	38(2)	37(2)	-4(1)	-9(1)	-5(2)
O(2)	50(2)	31(2)	43(2)	-8(1)	13(1)	4(2)
O(3)	55(2)	40(2)	28(1)	-4(1)	5(1)	-1(2)
O(4)	90(3)	38(2)	40(2)	-1(2)	14(2)	15(2)
N(1)	78(3)	34(2)	35(2)	1(2)	16(2)	20(2)
N(2)	79(3)	33(2)	34(2	1(2)	-1(2)	-6(2)
N(3)	49(2)	29(2)	25(2	-1(1)	8(1)	-2(2)
N(4)	54(3)	40(2)	32(2	-4(2)	4(2)	-6(2)
C(1)	50(3)	51(3)	52(3	-4(2)	13(2)	8(3)
C(2)	65(3)	34(3)	44(3	-4(2)	10(2)	14(2)
C(3)	54(3)	31(3)	41(2)	-3(2)	5(2)	12(2)
C(4)	57(3)	44(3)	52(3	-2(2)	6(2)	6(3)
C(5)	66(4)	34(3)	70(3	-5(3)	3(3)	2(3)
C(6)	67(4)	43(3)	61(3	-14(2)	8(3)	9(3)
C(7)	83(4)	71(5)	76(4	-4(3)	32(3)	15(3)
C(8)	52(3)	29(3)	33(2	0(2)	4(2)	-2(2)
C(9)	47(3)	28(3)	30(2	-3(2)	4(2)	2(2)
C(10	60(3)	31(3)	34(2	1(2)	5(2)	-6(2)
C(11)	89(4)	38(3)	36(3	5(2)	-9(2)	2(3)
C(12)	72(4)	32(3)	41(3)	1(2)	-1(2)	12(3)
C(13)	44(3)	26(2)	28(2	4(2)	7(2)	6(2)
C(14)	42(3)	39(3)	50(3	-2(2)	7(2)	-5(2)
C(15)	53(4)	62(4)	68(3	-1(3)	-4(3)	-6(3)
C(16)	69(4)	58(4)	65(3)	8(3)	16(3)	-18(3)
Li(1)	68(5)	30(4)	30(3	-4(3)	9(3)	0(4)

Table 6. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3)

	x	y	z	U
H(1O4)	5930(40)	4460(30)	2820(40)	67
H(2O4)	5490(40)	4800(30)	4040(50)	67
H(1N1)	6790(40)	480(30)	1160(40)	58
H(1N4)	7990(30)	2700(30)	480(40)	50
H(2)	8343	110	-136	57
H(4)	6524	-1559	1875	61
H(5)	7202	-2653	532	68
H(6)	8362	-2368	-1167	68
H(7A)	9080	-1161	-2801	91
H(7B)	10005	-1159	-1571	91
H(7C)	9398	-308	-2002	91
H(10)	5602	1375	5349	50
H(11)	7067	-779	6164	66
H(12)	7459	945-	3880	58
H(14)	8240(30)	3960(30)	2110(40)	54(13)
H(15A)	10100	3748	3019	74
H(15B)	10004	2784	2569	74
H(15C)	9275	3149	3719	74
H(16A)	9662	4290	536	76
H(16B)	8673	3893	-369	76
H(16C)	9698	3333	42	76

Torsemide lithium hydrate also gives distinctive X-ray powder diffraction pattern, as depicted in Figure 2. The pattern has characteristic peak (expressed in degree $2\theta \pm 0.2$) at about 7.2. Preferably, the peaks 7.2 and 9.2 are unique to torsemide lithium hydrate. Most preferably, the peaks 7.2, 9.2, 16.1, and 21.1 are unique to torsemide lithium hydrate.

The results of a single crystal X-ray analysis are limited to, as the name implies, to one crystal placed in the X-ray beam. Crystallographic data on a large group of crystals provides powder X-ray diffraction. If the powder consists of a pure crystalline compound, a simple powder diagram is obtained. To compare the results of a single crystal analysis and a powder X-ray analysis, a simple calculation can be done converting the single crystal analysis and powder X-ray diagram. This conversion is possible because the single crystal experiment routinely determines the unit cell dimensions, space group, and atomic positions. These parameters provide a basis to calculate a perfect powder pattern. Comparing this calculated powder pattern and the powder pattern experimentally obtained from a large collection of crystals will confirm if the results of the two techniques are the same. This has been done for torsemide lithium hydrate and the results are graphically displayed in Figures 2 and 3 and in Table 7.

Table 7. Calculated from single crystal X-ray analysis powder diffraction pattern (λ = 1.5418 Å radiation) where in I/I_1 represents the relative intensity:

2θ (°)	I/I_1	h	k	l	2θ (°)	I/I_1	h	k	l
7.148	.100	0	0	1	22.096	0.59	2	2	0
9.116	.305	0	1	1	22.301	.104	0	1	3
5.408	.125	0	1	2	24.408	.58	0	2	3
16.096	.476	-1	2	1	24.678	.97	1	3	2
17.528	.78	-1	1	2	24.882	.110	1	1	3
18.469	.73	0	3	1	25.513	.77	-1	4	1
18.641	.126	1	2	2	25.911	.66	1	4	1
21.015	.61	1	3	1	26.979	.124	0	4	2
21.099	.174	1	2	2	27.584	.68	0	3	3
21.511	.189	2	1	1	29.738	.53	1	3	3

Fig. 2 shows experimentally derived X-ray powder diffraction pattern of torsemide lithium hydrate and Fig. 3 corresponds to the X-ray diffraction pattern derived from the single crystal X-ray data. The peak overlap indicates that the two techniques yield the same results. The primary powder X-ray diffraction peaks provide an unambiguous description of the crystalline state of torsemide lithium hydrate.

A pure crystalline organic compound has, in general, a definite melting point range. The melting point is defined as the point at which the sample is entirely in the liquid phase. The crystalline torsemide lithium hydrate is characteristic melting point range determined by the capillary method from 180 to 186 °C (dec.).

The crystalline torsemide lithium hydrate was further characterized by an infrared absorption spectrum in potassium bromide pattern substantially as depicted in Fig. 4.

This invention will be better understood from the Examples that follow. However, the examples illustrate, but do not limit, the invention. Those skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims that follow thereafter.

EXAMPLES

Experimental details:

HPLC was carried out on a Merck-Hitachi Lachrom chromatographic system with UV detector (column: Inertsil ODS-3V; eluent: 0.1% TFA in acetonitrile / 0.1% TFA in water 28/78 v/v)

Single crystal x-ray crystallographic analysis was performed on a Phillips PW 11000 diffractometer, $\omega/2\theta$ mode, graphite monochromator, MoK_α radiation.

Powder x-ray diffraction patterns were obtained by methods known in the art using a Philips analytical x-ray powder diffractometer for wide-angle x-ray diffraction (CuK_α radiation of γ = 1.5418 Å, monochromator before detector, Pw3020 goniometer system). The Bragg-Brentano scheme was used for beam focusing.

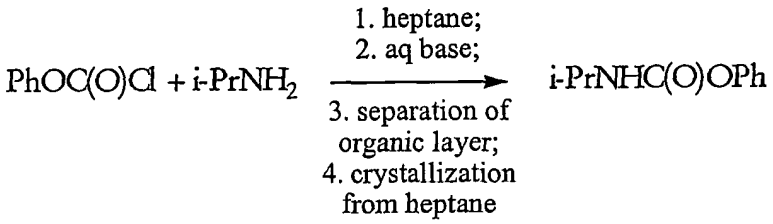
Melting points were determined in open capillary tubes with Electrothermal IA 9300 Digital capillary melting point apparatus and are uncorrected. The melting points of torsemide lithium hydrate generally depend upon their level of purity. Typically, torsemide lithium hydrate has been found to have a melting point between 180 and 186 °C.

Infrared spectra were recorded on a Nicolet Impact 410 FT-IR spectrophotometer using a 0.5 % dispersion of sample material in a potassium bromide disk over the wave number range 4000 to 400 cm^{-1}.

DSC graphs were recorded on a Mettler DSC 30 Differential Scanning Calorimeter.

Example 1

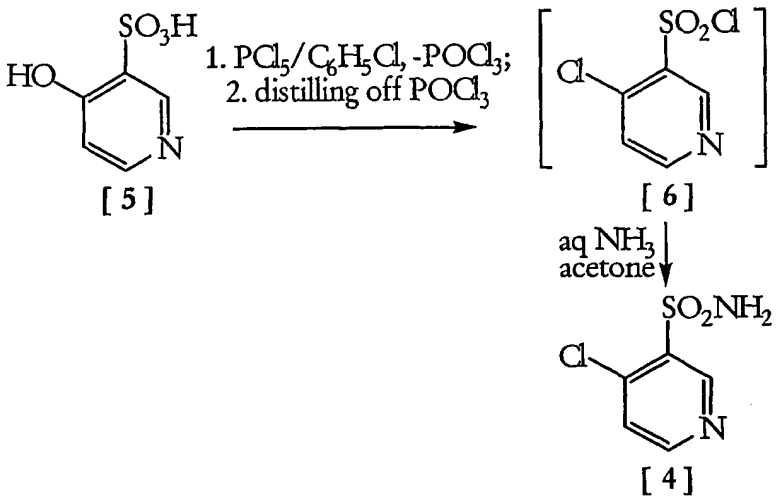
Phenyl N-isopropylcarbamate



A 1-L reactor was charged with isopropylamine (19.3 g, 0.33 mol) and heptane (196 g) and filled with nitrogen. A solution of phenyl chloroformate, (50.0 g, 0.32 mol) in heptane (34 g) was added dropwise to the stirred mixture at 0 - 4 °C. The obtained mixture was stirred for an hour at the same temperature. A solution of sodium hydroxide (11.7 g, 0.29 mol) in water (77 g) was added dropwise to the stirred mixture at 0 – 4 °C. The mixture was stirred at 60 - 70 °C until a complete dissolution. The organic layer was isolated, washed with hot water (78 g) at 60 - 70 °C and stirred for 2 hours at 0 – 5 °C. The precipitated solids were filtered off, washed on the filter with heptane (50 g), dried under reduced pressure at 40 - 50 °C (water bath) to give 46.1 g (80.6 %) of phenyl N-isopropylcarbamate with mp 81 – 82 °C and 99.7 % purity by GC.

Example 2

4-Chloro-3-pyridinesulfonamide **[4]**. "One-pot" procedure:

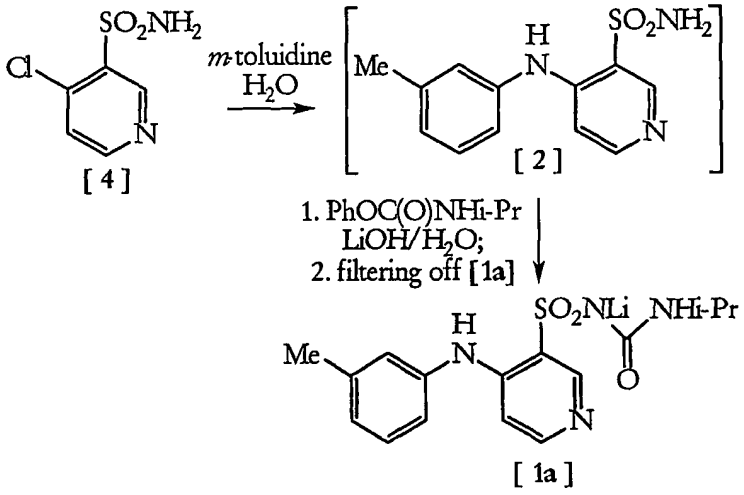


[5] [6] [4]

A mixture of 4-hydroxy-3-pyridinesulfonic acid **[5]** (50.0 g, 0.29 mol), phosphorus pentachloride (130.8 g, 0.63 mol) and chlorobenzene (580 g) was stirred under reflux conditions for 6 hours. The mixture of phosphorus oxychloride and chlorobenzene (590 – 610 g) were distilled off from the mixture at atmospheric pressure. The cooled (25 – 30 °C) residue (~100 mL) was added dropwise to the stirred mixture of 25 % aqueous ammonia (116.5 g, 1.7 mol) and acetone (20 g) for 30 - 40 minutes maintaining the temperature at 0 - 5 °C. The reaction mixture (pH 11 - 12) was stirred for 1 hour at the same temperature and for 1 hour at 25 °C. Chlorobenzene (50 g) and water (150 g) were added to the stirred mixture at the same temperature. The reaction mixture was concentrated to 250 – 300 g (pH 7 – 8) under reduced pressure (20 - 100 mbar) at 30 - 40 °C. The obtained suspension was stirred for 5 hours at 0 - 5 °C. The precipitated solids were filtered off, triturated with water (2 x 200 g) at 30 °C and dried under reduced pressure at 40 – 50 °C (water bath) to a constant weight to give 42.7 g (77.6 %) of 4-chloro-3-pyridinesulfonamide **[4]** with 99.6 % purity by HPLC, assay 99.9 % by $HClO_4$ titration, 0.06 % of water by KF titration and mp 146 – 148 °C (dec.).

Example 3

Torsemide lithium salt **[1a]**. "One-pot" procedure

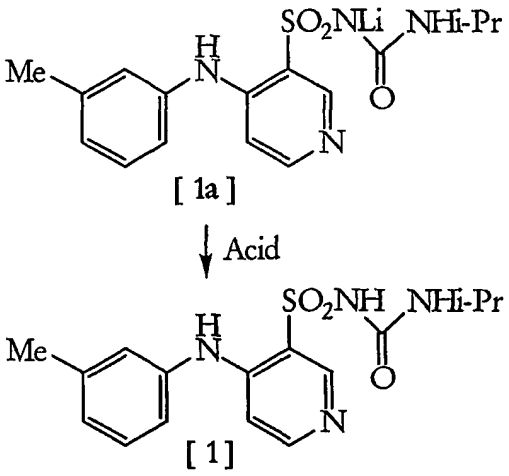


A mixture of 4-chloro-3-pyridinesulfonamide **[4]**, yellow powder with 95.0 % assay and 98.0 % purity by HPLC (100.0 g, 0.52 mol), *m*-toluidine (61.0 g, 0.57 mol) and water (600 g) was stirred at 80 - 90 °C for 1 hour. Lithium hydroxide monohydrate (45.6 g, 1.09 mol) was added to the stirred mixture at 25 - 40 °C. The mixture was stirred at the same temperature to a complete dissolution of the solids and the resulting mixture was extracted with toluene (3 x 180 g).

A solution of phenyl N-isopropylcarbamate (125.6 g, 0.70 mmol) in acetone (216 g) was added to the stirred aqueous solution at 25 - 30 °C. The mixture was stirred for 1 hour at 65 - 75 °C. An additional amount of lithium hydroxide monohydrate (4.4 g, 0.10 mol) was added to the mixture at 65 - 75 °C. The mixture was stirred for 1 hour at 65 - 75 °C and for 12 hours at 45 - 50 °C. The precipitated solids were filtered off, washed on the filter with water (500 g), triturated three times for 1 hour with hot (40 °C) acetone (400 g) and dried under reduced pressure at 50 - 60 °C (water bath) to a constant weight to give 133.2 g (68.8 %) of torsemide lithium salt **[1a]** as a white solid with 5.5 % of water by KF titration, 99.95 % purity by HPLC.

Example 4

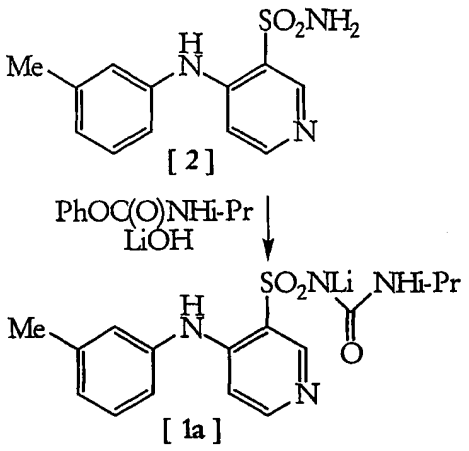
Torsemide **[1]**



Lithium torsemide (80.0 g, 0.22 mol) was dissolved in a stirred mixture of acetic acid (16.3 g, 0.27 mol) and DMSO (96.0 g) at 20 – 30 °C (1 hour). The solution was added dropwise to water (600 g) under vigorous stirring at 0 - 5 °C. The obtained suspension was stirred for 12 hours at the same temperature. The precipitated solids were filtered off, triturated with water (3 x 240 g) at 0 - 5 °C and dried under reduced pressure at 45 - 50 °C (water bath) to a constant weight to give 69.1 g of torsemide form II (powder X-ray and IR spectrum) with 99.95 % purity by HPLC.

Example 5

Preparation of lithium torsemide **[1a]**



A mixture of 4-*m*-toluidino-3-pyridinesulfonamide **[2]**, yellow powder with 95.0 % assay and 98.0 % purity by HPLC (7.5 g, 26.0 mmol), lithium hydroxide monohydrate (11.4 g, 27.2 mmol) and water (32 g) of was stirred at 25 - 35 °C to a complete dissolution of the solids and the resulting mixture was extracted with toluene (3 x 9 g).

A solution of phenyl N-isopropylcarbamate (6.3 g, 35.0 mmol) in acetone (10.8 g) was added to the mixture. The obtained mixture was stirred for 18 hours at 65 - 75 °C and 0.5 hour at 45 °C. The precipitated solids were filtered, washed on the filter with acetone (3 x 10 g) at 40 °C and dried under reduced pressure at 50 - 60 °C (water bath) to a constant weight to give 6.5 g of lithium torsemide **[1a]** as a white solid with 99.9 % purity by HPLC.

Example 6

Purification of lithium torsemide.

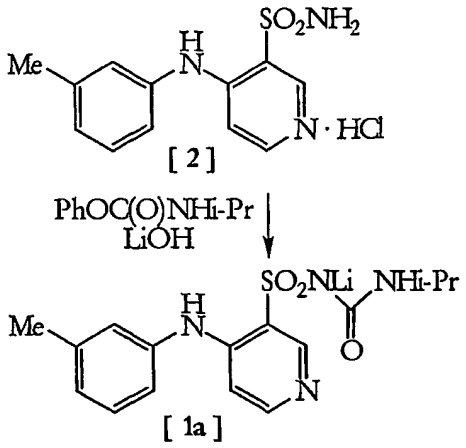
Lithium torsemide 99.7 % purity by HPLC (0.6 g) was dissolved in DMSO (2 mL) and filtered. The resulting solution was added dropwise to water (10 mL) and white crystals were formed. The precipitated crystals were filtered off, washed on filter with water (3 mL) and dried under reduced pressure to give crystalline torsemide lithium hydrate with 99.9 % purity by HPLC and mp 180 –186 °C (dec).

The torsemide lithium hydrate was characterized by power X-ray and IR absorption analysis as set forth above and in **Fig. 2** and **4**.

Single crystal of the torsemide lithium hydrate was isolated and used for determination crystallographic parameters (see **Tables 1-6**).

Example 7

Lithium torsemide **[1a]**

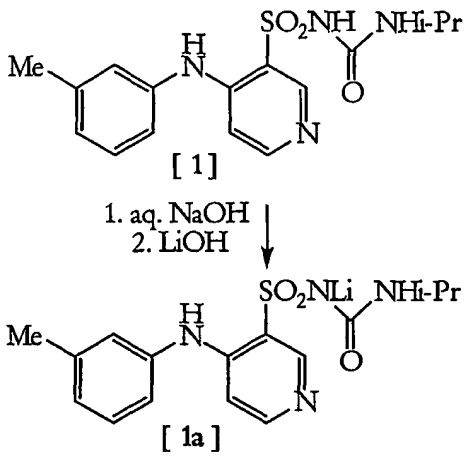


A mixture of 4-*m*-toluidino-3-pyridinesulfonamide hydrochloride **[2a]**, yellow powder with 95.0 % assay and 98.0 % purity by HPLC (7.5 g, 26.0 mmol), lithium hydroxide monohydrate (11.4 g, 27.2 mmol) and water (32 g) of was stirred at 25 - 35 °C to a complete dissolution of the solids and the resulting mixture was extracted with toluene (3 x 9 g).

A solution of phenyl N-isopropylcarbamate (6.3 g, 35.0 mmol) in acetone (10.8 g) was added to the mixture. The obtained mixture was stirred for 18 hours at 65 - 75 °C and 0.5 hour at 45 °C. The precipitated solids were filtered, washed on the filter with acetone (3 x 10 g) at 40 °C and dried under reduced pressure at 50 - 60 °C (water bath) to a constant weight to give 6.5 g of lithium torsemide **[1a]** as a white solid with 99.9 % purity (0.1 % of 4-*m*-toluidino-3-pyridinesulfonamide **[2]**) by HPLC.

Example 8

Lithium torsemide **[1a]**

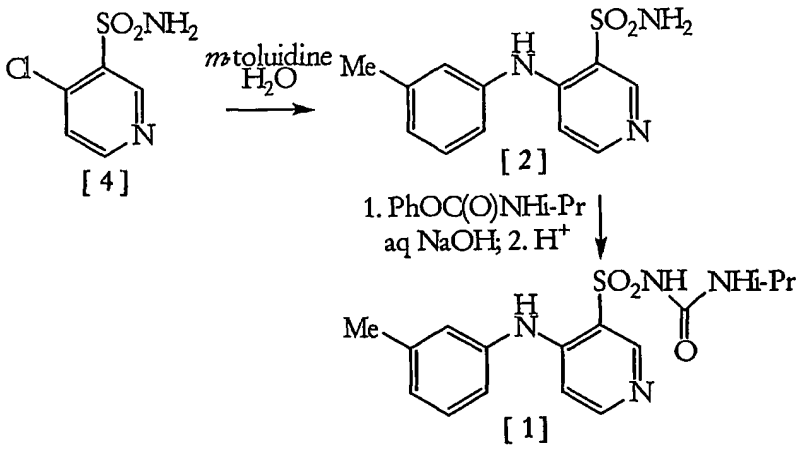


A mixture of torsemide **[1]**, yellow powder with 95.0 % assay and 98.0 % purity by HPLC (7.5 g, 26.0 mmol), sodium hydroxide (10.9 g, 27.2 mmol) and water (32 g) of was stirred at 25 - 35 °C to a complete dissolution of the solids and the resulting mixture was extracted with butyl acetate (3 x 9 g).

Lithium hydroxide monohydrate (11.4 g, 27.2 mmol) was added to the mixture. The obtained mixture was stirred for 2 hours at 25 - 35 °C. The precipitated solids were filtered, washed on the filter with acetone (3 x 10 g) at 40 °C and dried under reduced pressure at 50 - 60 °C (water bath) to a constant weight to give 6.5 g of lithium torsemide **[1a]** as a white solid with 99.9 % purity (0.1 % of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**) by HPLC.

Example 9

Torsemide **[1]**. "One-pot" procedure



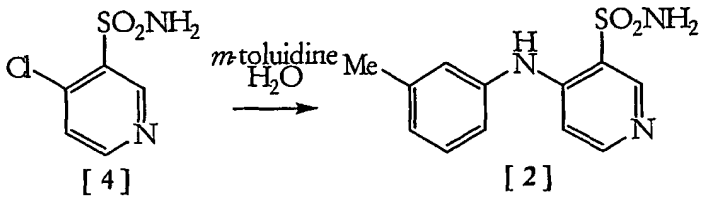
A mixture of 4-chloro-3-pyridinesulfonamide **[4]**, yellow powder with 95.0 % assay and 98.0 % purity by HPLC (50.0 g, 260 mmol), *m*-toluidine (30.5 g, 285 mmol) and water (230 g) was stirred at 80 - 85 °C for 1.5 hour. A solution of sodium hydroxide (21.8 g, 545 mmol) in water (33 g) was added dropwise to the stirred mixture at 25 -35 °C. The mixture was stirred at 20 - 30 °C to a complete dissolution of the solids and the resulting mixture was extracted with toluene (3 x 90 g).

A solution of phenyl N-isopropylcarbamate (62.8 g, 350 mmol) in acetone (108 g) was added to the mixture and then was stirred for 20 hours at 50 - 60 °C. Water (100 g) was added to the stirred mixture at 20 - 25 °C. The mixture was extracted with butyl acetate (180 g then 3 x 90 g) and slowly (during 2 hours) acidified at 15 - 20 °C to pH 7.0 with a solution of 96 – 98 % sulfuric acid (13.0 g, 135 mmol) in water (247 g). The obtained suspension was stirred for 1 hour at 50 °C (pH 7). The precipitated solids were filtered, washed on the filter with a mixture of acetone (125 g) and water (125 g) and dried under reduced pressure at 50 - 60 °C (water bath) to a constant weight to give 70.9 g (78.4 %) of crude torsemide as a white solid with 99.4 % purity (0.10 % of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**) by HPLC.

A solution of sodium hydroxide (8.7 g, 218 mmol) in water (217 g) was added dropwise to the stirred suspension of the crude torsemide (70.0 g, 201 mmol) and water (630 g) at 20 - 30 °C. The mixture was stirred at 20 - 30 °C to a complete dissolution of the solids (pH 12.9) and charcoal SA (7.0 g) was added. After stirring for 2 hours, the obtained mixture was filtered, cooled to 15 - 20 °C and acidified to pH 4.6 with a 5 % solution of sulfuric acid in water (28.2 g, 14 mmol) at the same temperature. The obtained suspension was stirred for 2 hours at 15 - 20 °C. The precipitated solids were filtered, washed on the filter with water (2 x 150 g) and dried under reduced pressure at 55 ± 5 °C (water bath) to a constant weight to give 62.4 g (69 %) of torsemide **[1]** as a white solid with 99.8 % purity by HPLC.

Example 10

Preparation of 4-*m*-toluidino-3-pyridinesulfonamide **[2]**

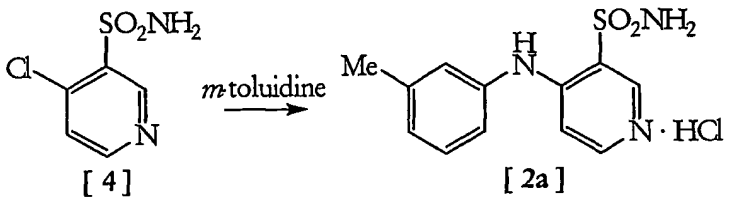


[4] [2]

A mixture of 4-chloro-3-pyridinesulfonamide **[4]**, yellow powder with 95.0 % assay and 98.0 % purity by HPLC (1.0 g, 5.2 mmol), *m*-toluidine (0.6 g, 5.7 mmol) and water (3.0 mL) was stirred under reflux conditions for 0.5 hour. 1 N aqueous solution of sodium hydroxide (12.0 mL, 12 mmol) was added dropwise to the stirred mixture at 25 -35 °C. The mixture was stirred at 20 - 30 °C to a complete dissolution of the solids and the resulting mixture was extracted with toluene (3 x 5 g). The aqueous layer was neutralized with 1 N aqueous solution of sulfuric acid. The precipitated solids were filtered, washed on the filter with water (2 x 10 mL) and toluene (10 mL) and dried under reduced pressure at 50 – 60 °C (water bath) to a constant weight to give 1.4 g (100 %) of 4-*m*-toluidino-3-pyridinesulfonamide **[2]** as an off-white powder with 99.0 % purity (0.5 % of 4-chloro-3-pyridinesulfonamide **[4]**) by HPLC.

Example 11

Preparation of 4-*m*-toluidino-3-pyridinesulfonamide hydrochloride **[2a]**

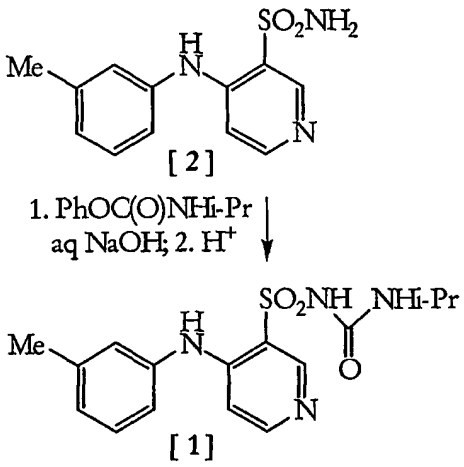


[4] [2a]

A mixture of 4-chloro-3-pyridinesulfonamide **[4]**, yellow powder with 95.0 % assay and 98.0 % purity by HPLC (18.0 g, 94.3 mmol), *m*-toluidine (11.0 g, 103 mmol) and methyl ethyl ketone (110 mL) was stirred under for 1.5 hours reflux conditions and for 1 hour at 20 – 25 °C. The precipitated solids were filtered off, washed on the filter with methyl ethyl ketone (18 g) and dried under reduced pressure at 50 – 60 °C (water bath) to a constant weight to give 25.6 g (91.4 %) of 4-*m*-toluidino-3-pyridinesulfonamide hydrochloride **[2a]** as an off-white powder with 99.0 % purity (0.5 % of 4-chloro-3-pyridinesulfonamide **[4]**) by HPLC.

Example 12

Preparation of torsemide **[1]**



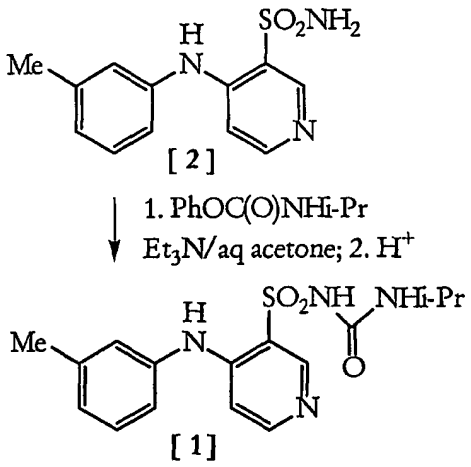
A mixture of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**, yellow powder with 98.0 % purity (0.5 % of 4-chloro-3-pyridinesulfonamide **[4]**) by HPLC (5.0 g, 19 mmol), 1 N aqueous solution of sodium hydroxide (19 mL, 19 mmol) and phenyl isopropylcarbamate (5.1 g, 23 mmol) was stirred at 90-100 °C for 5 hours diluted with water (20 mL), cooled to 20 – 25 °C, extracted with *tert*-butyl methyl ether (4 x 30 mL), neutralized with an 1 N aqueous solution of sulfuric acid at 20 - 25 °C and stirred for 1 hour at 60-70 °C. The precipitated solids were filtered off, washed on filter with hot water (20 mL) and acetone (20 mL) to give 5.6 g (85 %) of crude torsemide **[1]** 99.4 % purity (0.1 % of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**) by HPLC.

A solution of sodium hydroxide (0.62 g, 16 mmol) in water (15 g) was added to a stirred suspension of crude torsemide **[1]** (5.0 g, 14 mmol) in water (45 g) at 20 - 30 °C. The mixture was stirred at 20 - 30 °C until a complete dissolution of the solids (pH 12.9) and charcoal SA (0.5 g) was added to the solution. After stirring for 2 hours, the obtained mixture was filtered off,

cooled to 15 - 20 °C and acidified to pH 4.6 with a 1 N solution of sulfuric acid in water (~28 mL, 28 mmol) at the same temperature. The obtained suspension was stirred for about 2 hours at 15 - 20 °C and filtered. The solid was washed on the filter with water (50 g) and dried under reduced pressure at 55 ± 5 °C (water bath) to a constant weight to give 4.7 g of torsemide [1] as a white solid with 99.4 % purity by HPLC.

Example 13

Torsemide **[1]**

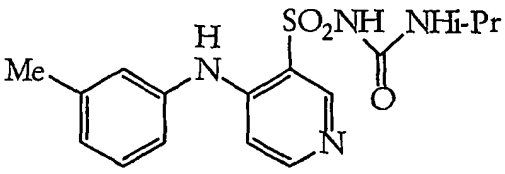


A mixture of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**, yellow solid with 99.4 % purity (0.2 % of 4-chloro-3-pyridinesulfonamide **[4]**) (5.0 g, 19 mmol), triethylamine (2.9 g, 28 mmol), phenyl isopropylcarbamate (5.0 g, 28 mmol), acetone (12.5 mL) and water (12.5 mL) was stirred under reflux conditions for 3 hour. Acetone was distilled off from the mixture. The residue was basified with 1 N aqueous sodium hydroxide (20 mL, 20 mmol) at 20 - 25 °C, diluted with water (20 mL) and extracted with *tert*-butyl methyl ether (4 x 50 mL). The water layer was diluted with acetone (10 mL), neutralized with 1 N aqueous sulfuric acid (20 mL, 20 mmol). The resulting suspension was stirred for 1 hour at 50 – 55 °C. The precipitated solids were filtered off, washed on filter with a mixture of acetone (12.5 mL) and water (12.5 mL), dried under reduced pressure at 40 - 50 °C to a constant weight to give 5.8 g (87.8 %) of torsemide **[1]** as a white solid with 99.4 % purity by HPLC.

Although certain presently preferred embodiments of the invention have been described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the described embodiments may be made without departing from the spirit and scope of the invention.

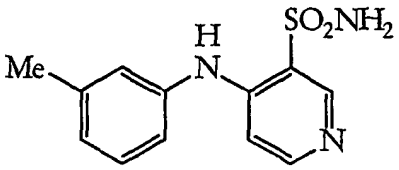
CLAIMS:

1. A process for the preparation of torsemide [1]

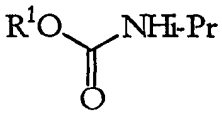


[1]

comprising reacting 4-*m*-tolylamino-3-pyridinesulfonamide [2] or its salt with isopropylcarbamate of formula [3]



[2]



[3]

optionally, in the presence of a base, wherein R^1 represents an aryl group, the aryl group being possibly substituted by one or more substituents selected from C1-C4-alkyl, alkoxy, halo, trifluoromethyl and nitro.

2. The process according to claim 1 which comprises the steps of:

(a) reacting 4-*m*-tolylamino-3-pyridinesulfonamide [2] with isopropylcarbamate of formula [3] in the presence of lithium base, water and an organic solvent to give lithium torsemide in solid form;

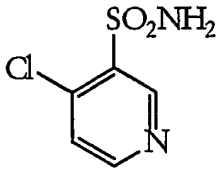
(b) filtering the precipitated lithium torsemide obtained in step (a); and, optionally, purifying of the lithium torsemide by recrystallizing, triturating or/and reslurring of said salt to give lithium torsemide

(c) acidifying the lithium torsemide obtained in step (b), to yield highly pure torsemide [1].

3. The process of claim 2, wherein the lithium base used in step (a) selected from lithium hydroxide, lithium carbonate, lithium bicarbonate and mixtures thereof.

4. The process according to claim 1 which comprises the steps of:

(a) reacting of 4-chloro-3-pyridinesulfonamide **[4]**



[4]

with excess of *m*-toluidine in aqueous media;

(b) basifying the reaction mixture with lithium hydroxide to form the lithium salt of 4-*m*-tolylamino-3-pyridinesulfonamide;

(c) extracting excess of *m*-toluidine from the mixture obtained in step (b) with organic solvent;

(d) reacting the aqueous solution of the lithium salt of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]** obtained in step (a) with isopropylcarbamate of formula **[3]** in the presence of an organic solvent to precipitate lithium torsemide; and, optionally, purifying of the lithium torsemide by recrystallizing, trituring or/and reslurring of said salt to give lithium torsemide :

(e) filtering off and acidifying the lithium torsemide obtained in step (d) to yield highly pure torsemide **[1]**.

5. The process according to anyone of claims 1 to 4 wherein the isopropylcarbamate of formula **[3]** is phenyl or nitrophenyl isopropylcarbamate.

6. The process according to claim 1, wherein R^1 represents a phenyl group, the phenyl group being possibly substituted by one or more substituents selected from the C1-C4-alkyl, alkoxy, halo, trifluoromethyl and nitro.

7. The process according to claim 1, wherein compound **[3]** wherein R^1 represents a phenyl group is prepared by a process comprising the steps of:

(i) reacting phenyl chloroformate and isopropylamine in the presence of heptane as solvent;

(ii) basifying the mixture obtained in step (i) with aqueous alkali;

(iii) separating the organic layer from the mixture obtained in step (ii);

(iv) washing the organic phase obtained in the step (iii) with water and azeotropic drying of the wet organic phase;

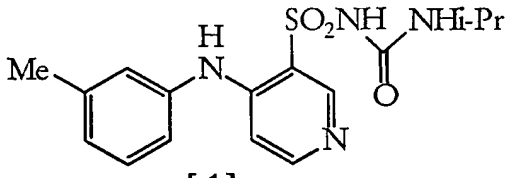
(v) crystallizing the desired product from the heptane solution and, optionally, recrystallizing phenyl isopropylcarbamate from heptane.

8. The process according to claims 2 or 4 wherein said organic solvent is selected from the group consisting of aliphatic ketones and aliphatic alcohols.

9. The process according to claim 8 wherein said aliphatic ketones are selected from acetone, methyl ethyl ketone (MEK), diethyl ketone, methyl isopropyl ketone and methyl isobutyl ketone (MIBK).

10. The process according to claim 8 wherein said aliphatic alcohols are selected from methanol, ethanol, isopropanol and butanol.

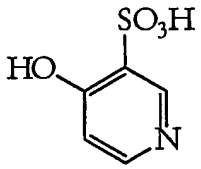
11. The process according to claim 4 for the preparation of torsemide **[1]**



[1]

wherein compound **[4]** is prepared by a process comprising the steps of:

(a) mixing 4-hydroxy-3-pyridinesulfonic acid **[5]**,



[5]

phosphorus pentachloride and chlorobenzene at 0 – 40 °C and stirring the mixture at a temperature higher than 80 °C;

(b) removing any phosphorous oxychloride formed in step (a) by distillation;

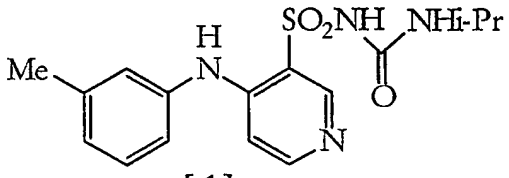
(c) adding the resulting solution of 4-chloro-3-pyridinesulfochloride **[6]**

[6]

in chlorobenzene to ammonia;

(d) evaporating any ammonia excess from the reaction mixture obtained in step (c) and isolating the precipitated solid 4-chloro-3-pyridinesulfonamide **[4]** by filtration.

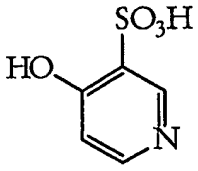
12. A process for the preparation of highly pure torsemide **[1]**



[1]

which process comprises the steps of:

(a) mixing 4-hydroxy-3-pyridinesulfonic acid **[5]**,



[5]

phosphorus pentachloride and chlorobenzene at 0 – 40 °C and stirring the mixture at 80 – 150 °C;

(b) removing any phosphorous oxychloride formed by distillation;

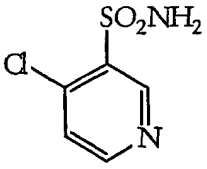
(c) adding the resulting solution of 4-chloro-3-pyridinesulfochloride **[6]**

in chlorobenzene to ammonia;

52

[6]

(d) evaporating any ammonia excess from the reaction mixture prepared in step (c) and isolating the precipitated solid 4-chloro-3-pyridinesulfonamide **[4]**



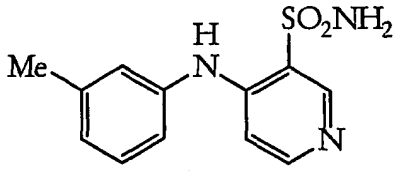
[4]

by filtration;

(e) reacting the 4-chloro-3-pyridinesulfonamide **[4]** prepared in step (d) with excess of *m*-toluidine in aqueous media;

(f) adding lithium hydroxide, lithium carbonate or lithium bicarbonate to the mixture of step (e) and removing any un-reacted *m*-toluidine by extraction, to obtain an aqueous solution of the lithium salt of **[2]**;

(g) reacting the aqueous solution of the lithium salt of 4-*m*-tolylamino-3-pyridinesulfonamide **[2]**



[2]

obtained on step (f) with aryl isopropylcarbamate **[3]** in the presence of organic solvent;

(h) isolating the precipitated solid lithium torsemide prepared in step (g) by filtration; and, optionally, purifying of the lithium torsemide by recrystallizing, triturating or/and reslurring of said salt to give lithium torsemide with purity of the least 99.8 % by HPLC;

(j) acidifying the lithium salt of torsemide prepared in step (h), to yield highly pure torsemide [1].

13. Lithium salt of torsemide.

14. Lithium salt of torsemide in solid form.

15. Torsemide lithium solvent adduct.

16. Crystalline torsemide lithium solvent adduct

17. Torsemide lithium solvent adduct of claim 15 or 16, wherein the solvent is selected from water, ethanol, isopropanol and isobutanol.

18. Torsemide lithium hydrate according to claim 16, which exhibits an X-ray powder diffraction pattern having characteristic peak expressed in degrees 2θ at about 7.2±0.2.

19. Torsemide lithium hydrate according to claim 16, which exhibits an X-ray powder diffraction pattern having characteristic peaks, expressed in degrees 2θ at about 7.2 and 9.2±0.2.

20. Torsemide lithium hydrate according to claim 16, which exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2θ at about 7.2, 9.2, 16.1, and 21.1±0.2.

21. Torsemide lithium hydrate according to claim 16, which exhibits an X-ray powder diffraction pattern substantially the same as that shown in Fig. 2.

22. Torsemide lithium hydrate according to claim 16, that exhibits a single crystal X-ray crystallographic analysis at 293 K with crystal parameters that are approximately equal to the following:

Space group	$P\ 2_1/c$
Cell dimensions	
a (Å)	12.401
b (Å)	15.640
c (Å)	9.408
α (°)	90.00
β (°)	94.22
γ (°)	90.00
V ($Å^3$)	1819.7
Z (molecules/units cell)	4
Density (g/cm^3)	1.359

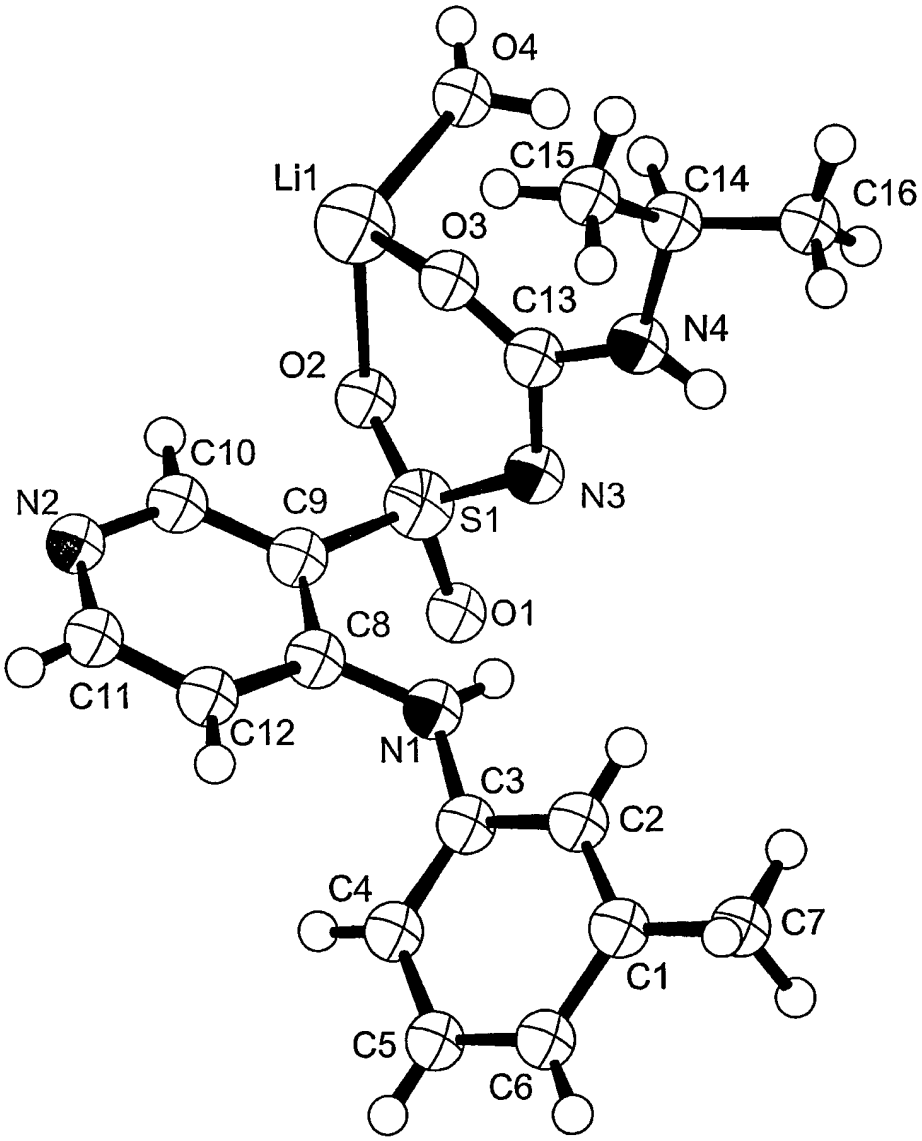

O4
C15
Li1
C14
C16
O3
C13
N4
O2
C10
N2
C9
S1
N3
O1
C8
C11
C12
N1
C3
C2
C4
C7
C1
C5
C6

FIG. 1

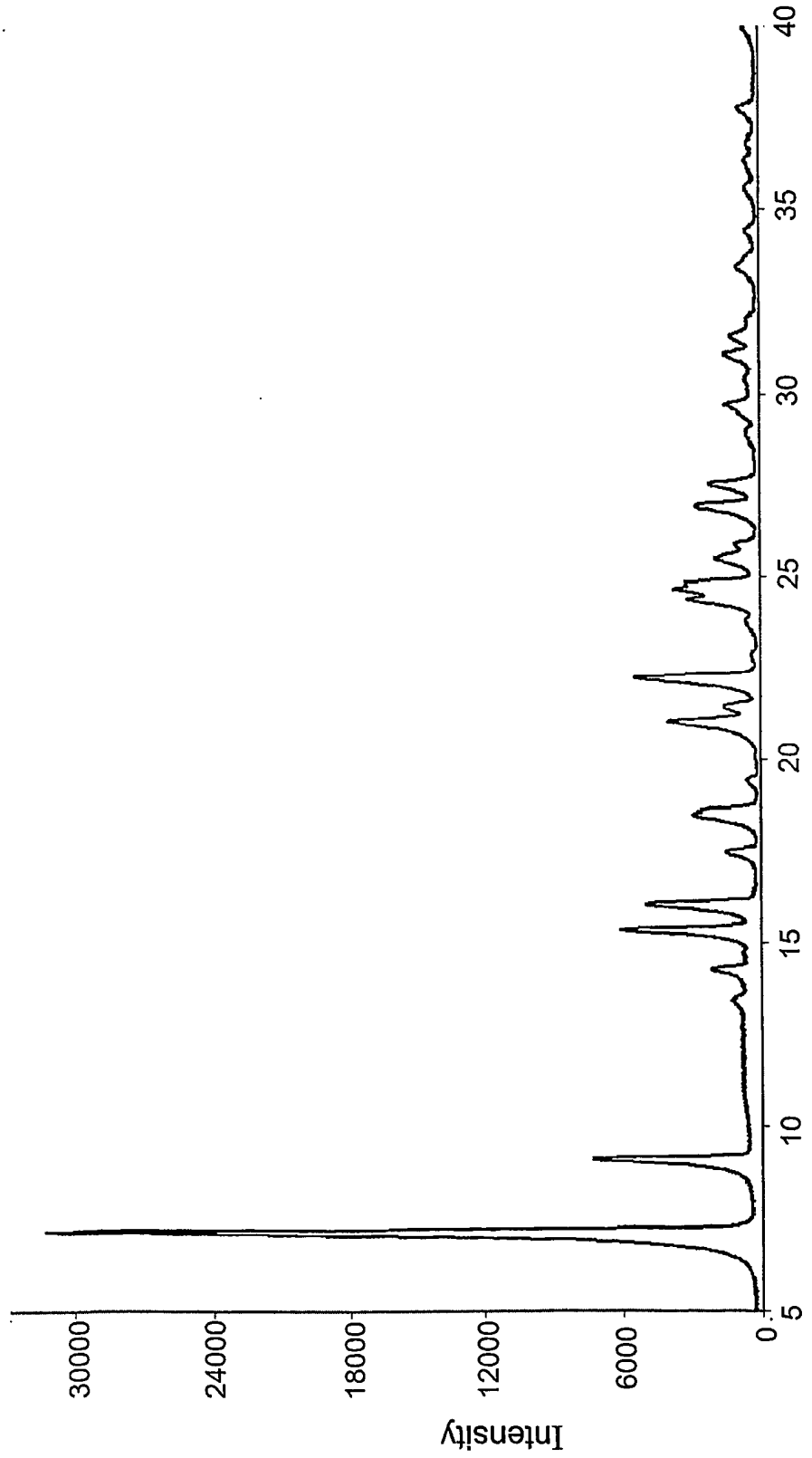

Intensity
30000
24000
18000
12000
6000
0
5
10
15
20
25
30
35
40
2-THETA (deg)

FIG. 2

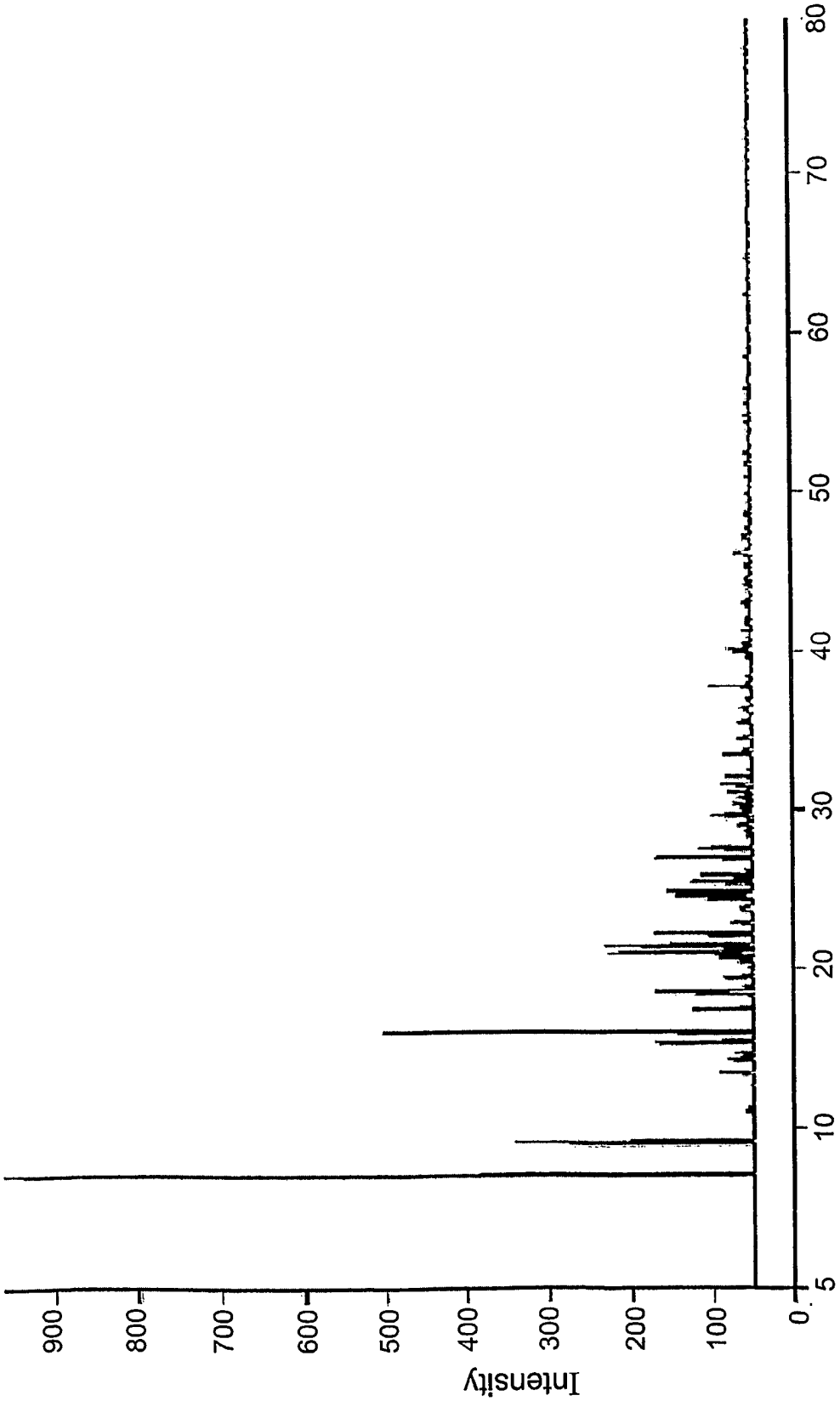

Intensity
900
800
700
600
500
400
300
200
100
0
5
10
20
30
40
50
60
70
80
2-THETA (deg)

FIG. 3

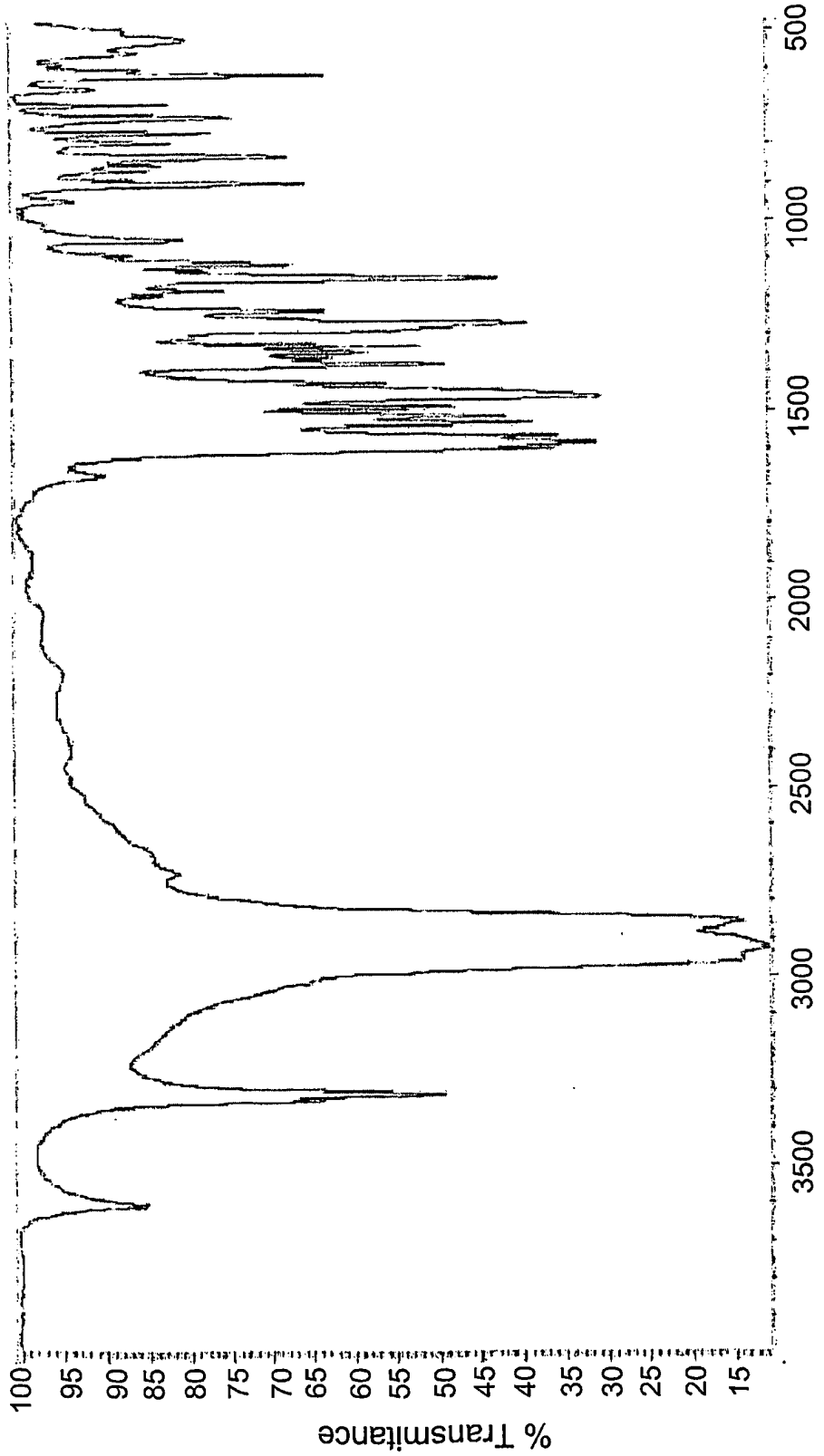

% Transmitance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

FIG. 4

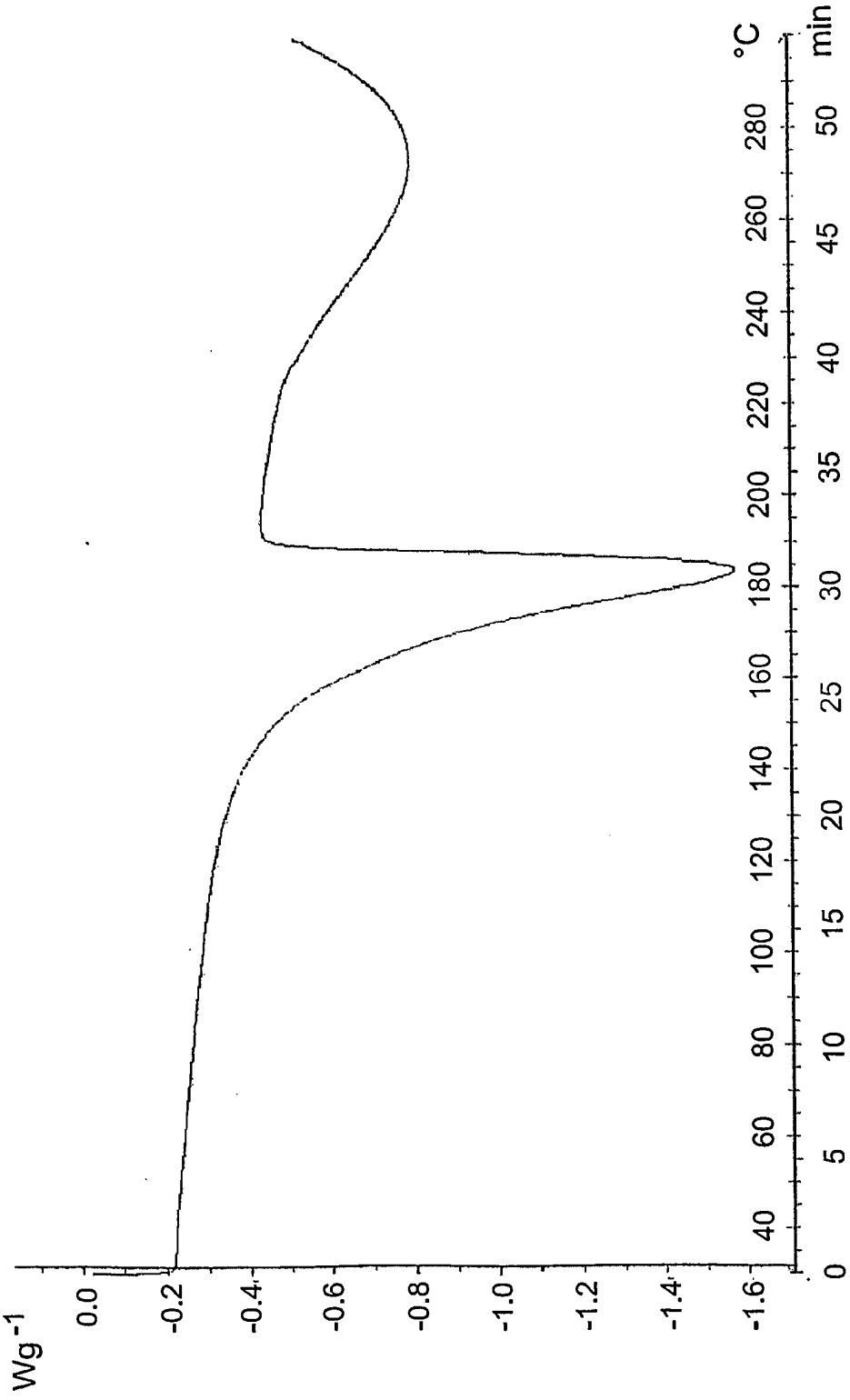

Wg-1
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
-1.6
40
60
80
100
120
140
160
180
200
220
240
260
280
°C
0
5
10
15
20
25
30
35
40
45
50
min

FIG. 5

INTERNATIONAL SEARCH REPORT

PCT/IL 03/00311

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/74 A61K31/44 A61P7/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 70226 A (KORDOVA MARCO ;TEVA PHARMA (IL); TEVA PHARMACEUTICALS USA INC (US)) 27 September 2001 (2001-09-27) claim 14; example 2	1-22
A	DE 25 16 025 A (CHRISTIAENS SA A) 6 November 1975 (1975-11-06) claim 10; example 71	1-22
A	US 4 244 950 A (DE RIDDER RENE R ET AL) 13 January 1981 (1981-01-13) example 1	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2003	20/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Menegaki, F

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